META-ANALYSES OF THE RELATION BETWEEN SILICONE BREAST IMPLANTS AND THE RISK OF CONNECTIVE-TISSUE DISEASES

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ABSTRACT

Background   The postulated relation between silicone breast implants and the risk of connective-tissue and autoimmune diseases has generated intense medical and legal interest during the past decade. The salience of the issue persists, despite the fact that a great deal of research has been conducted on this subject. To provide a stronger quantitative basis for addressing the postulated relation, we applied several techniques of meta-analysis that combine, compare, and summarize the results of existing relevant studies.

Methods   We searched data bases and reviewed citations in relevant articles to identify studies that met prestated inclusion criteria. Nine cohort studies, nine case–control studies, and two cross-sectional studies were included in our meta-analyses. We conducted meta-analyses of the results of these studies, both with and without adjustment for confounding factors, and a separate analysis restricted to studies of silicone-gel–filled breast implants. Finally, we estimated the annual number of new cases of connective-tissue disease that could be attributed to breast implants.

Results   There was no evidence that breast implants were associated with a significant increase in the summary adjusted relative risk of individual connective-tissue diseases (rheumatoid arthritis, 1.04 [95 percent confidence interval, 0.72 to 1.51]; systemic lupus erythematosus, 0.65 [95 percent confidence interval, 0.35 to 1.23]; scleroderma or systemic sclerosis, 1.01 [95 percent confidence interval, 0.59 to 1.73]; and Sjögren's syndrome, 1.42 [95 percent confidence interval, 0.65 to 3.11]); all definite connective-tissue diseases combined (0.80; 95 percent confidence interval, 0.62 to 1.04); or other autoimmune or rheumatic conditions (0.96; 95 percent confidence interval, 0.74 to 1.25). Nor was there evidence of significantly increased risk in the unadjusted analyses or in the analysis restricted to silicone-gel–filled implants.

Conclusions   On the basis of our meta-analyses, there was no evidence of an association between breast implants in general, or silicone-gel–filled breast implants specifically, and any of the individual connective-tissue diseases, all definite connective-tissue diseases combined, or other autoimmune or rheumatic conditions. From a public health perspective, breast implants appear to have a minimal effect on the number of women in whom connective-tissue diseases develop, and the elimination of implants would not be likely to reduce the incidence of connective-tissue diseases. (N Engl J Med 2000;342:781-90.)

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THE relation between silicone breast implants and autoimmune or connective-tissue diseases has been the focus of considerable medical and legal discussion throughout the past decade.[1-4] Concern was aroused by early case reports of connective-tissue disease in women who had received breast implants or silicone injections.[5,6] Three meta-analyses have failed to demonstrate an increased risk of specific connective-tissue diseases (rheumatoid arthritis, systemic lupus erythematosus, and scleroderma or systemic sclerosis) or connective-tissue diseases in general after implantation of silicone breast prostheses.[7-9] However, the meta-analyses to date leave some questions unanswered. Perkins et al.[7] performed a meta-analysis that dealt with unadjusted estimates of effect but did not consider the effect of adjustment for potential confounding factors. Wong[8] and Hochberg and Perlmutter[9] performed analyses of adjusted effects, but in neither study were formal statistical tests of homogeneity among studies undertaken, nor were analyses of the influence of individual studies or combinations of studies conducted. None of these meta-analyses focused exclusively on silicone-gel–filled breast implants. Moreover, eight new studies of the possible relation between silicone breast implants and autoimmune conditions or connective-tissue diseases have been published since 1996[10-17] and were not included in the previous meta-analyses.

We conducted a comprehensive series of meta-analyses of the largest group of studies to date to investigate the possible relation between silicone breast implants and the risk of autoimmune conditions or connective-tissue diseases. Our study incorporated the eight studies not included in the earlier meta-analyses and had four principal objectives: to investigate the relation between breast implants and connective-tissue diseases by incorporating all eligible studies into an unadjusted analysis; to consider the effect of potential confounding factors in an adjusted analysis; to search for sources of heterogeneity among the studies with formal statistical tests and influence analyses; and to perform a separate analysis focused exclusively on silicone-gel–filled breast implants.[18] In addition, we evaluated the public health effect of silicone breast implants by estimating the annual number of

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new cases of connective-tissue disease that can be attributed to the presence of breast implants.

METHODS

Selection of Studies

We obtained the results of studies cited in other meta-analyses and reviews,[7-9,19] and we conducted a search of the literature that was similar to that outlined by Perkins et al.[7] Sources included Medline (National Library of Medicine, Bethesda, Md.) from January 1966 through May 1998; Toxline (National Library of Medicine, Bethesda, Md.) from January 1985 through May 1998; Current Contents Search (Institute for Scientific Information, Philadelphia) from July 1997 through May 1998; and Dissertation Abstracts Online (University Microfilms International, Ann Arbor, Mich.) from January 1992 through May 1998. In searches of Medline, Toxline, and Current Contents Search, we used a combination of key words for breast implants and connective-tissue diseases. Key words for studies of breast implants included "breast implant," "breast augmentation," "breast reconstruction," "mammoplasty," and "mammaplasty," with all possible suffixes allowed (e.g., "implantation" and "implants"). Key words for connective-tissue diseases included "rheumatic diseases," "connective tissue disease," "autoimmune disease," "systemic sclerosis," "scleroderma," "lupus," "dermatomyositis," "sarcoidosis," "rheumatoid arthritis," "fibromyalgia," "Sjögren," and "polymyositis." A search of Dissertation Abstracts Online was conducted with use of a combination of key words for "breast implant" and "connective tissue disease." All searches were limited to studies of human subjects and reports published in English; they produced 757 citations. We were unable to obtain one abstract[20] that had appeared in 1993 and was cited in two publications.[8,19]

All the potentially relevant papers were reviewed independently by the investigators. The criteria for inclusion in the meta-analyses were the presence of an internal comparison group and the availability of numbers for the construction of two-by-two tables to establish categories of disease and implants. In cases in which there was more than one published report on the same population or group of patients, the most recent article was selected for analysis. Studies reporting only information on symptoms and the frequency with which individual symptoms appeared were excluded, since individual women, not individual symptoms, were the units of analysis.

Abstraction of Data

All the data were independently abstracted by two investigators with the use of standardized data-abstraction forms. Disagreements were resolved by discussion. The following information was sought from each paper, although some papers did not contain all the information: first author's name, year of publication, geographic location of the study, source of funding for the study, type of study design (cohort, case–control, or cross-sectional), study population, sample size, source of subjects (private practice, tertiary care center, or defined population), type of implant, date of implantation, reason for implantation (cosmetic or reconstructive), disease diagnosis, case definition, date of diagnosis, method of data collection (self-report or medical-record abstraction), average time to onset of symptoms after implantation, control for confounding factors by matching or adjustment, and relative risks or odds ratios and 95 percent confidence intervals for individual connective-tissue diseases and all connective-tissue diseases combined associated with all types of breast implants and with silicone-gel–filled breast implants alone, if analyzed separately.

Diseases Studied

The following disease entities were included in the analyses: rheumatoid arthritis; systemic lupus erythematosus; scleroderma or systemic sclerosis; Sjögren's syndrome; dermatomyositis or polymyositis; all definite connective-tissue diseases combined, as defined in each study; and a category of other autoimmune or rheumatic

conditions. The category of other autoimmune or rheumatic conditions included conditions, such as undifferentiated connective-tissue disease or mixed connective-tissue disease, that did not fulfill the diagnostic criteria of the classic autoimmune diseases or connective-tissue diseases; this category also included signs and symptoms of autoimmune or rheumatic conditions, such as joint pain, swelling, or both, as determined by the authors of each study.

Statistical Analysis

The disease variables were as follows: the presence or absence of any of the five individual connective-tissue diseases, the presence or absence of all definite connective-tissue diseases combined, and the presence or absence of other autoimmune or rheumatic conditions. The exposure variable was the presence or absence of any type of breast implant. Women who had had direct injections of any material into the breast, including silicone, were excluded from the analysis. A separate analysis was conducted for implants described in the individual studies as silicone-gel–filled breast implants.

We used fixed-effects models, as described by Greenland,[21] as opposed to random-effects models, in our meta-analyses.

Unadjusted Analyses

The basic data used in the unadjusted analyses consisted of a series of two-by-two tables defined by the dichotomous exposure and disease variables for each study. Because the numbers in some cells of the two-by-two tables were small, exact analyses and conditional maximum-likelihood methods were used.[22] Separate analyses of the associations in two-by-two tables were combined to produce summary estimates of the odds ratio with exact confidence limits.[22] Summary estimates of the odds ratio and associated tests for homogeneity were calculated for all connective-tissue diseases combined, for specific diseases, and for other autoimmune or rheumatic conditions. We used stratified analyses involving three dichotomous variables (cohort design vs. other study design, year of diagnosis before 1992 vs. year of diagnosis 1992 or later, and validation of disease through medical records vs. no validation of disease through medical records), as well as influence analysis, to search for sources of heterogeneity. Summary odds ratios were calculated with the use of Exact statistical software.[22]

Adjusted Analyses

Only studies that provided an adjusted estimate, either through the use of appropriate methods of analysis or through matching of variables in the study design, were considered in this analysis. The data needed from each study were the estimated adjusted effect (either the adjusted relative risk or the adjusted odds ratio, the latter being a good approximation of the adjusted relative risk in the case of rare diseases) and its estimated standard error (often obtained indirectly from the confidence interval reported in the study). First, we decided whether the adjusted relative risks from each study were estimating the same underlying association between exposure and disease. We used a chi-square test for homogeneity to help us make this decision.[21] If the test for homogeneity was not rejected at a P value ≤0.10, we computed an estimated summary adjusted relative risk involving an inverse-variance–based weighted average of the individual natural logarithms of the values for adjusted relative risk.[21] Larger studies producing estimated adjusted effects with smaller standard errors were weighted more heavily in the summary adjusted relative risks than smaller studies with correspondingly larger standard errors. Using the same methods of analysis, we produced an additional meta-analysis of silicone-gel–filled implants only. SAS statistical software (version 6.12, SAS Institute, Cary, N.C.) was used to calculate the estimates of the summary adjusted relative risks.

RESULTS

We included nine cohort studies,[10,11,15,16,23-27] nine case–control studies,[13,14,17,28-33] and two cross-section-

TABLE 1. CHARACTERISTICS OF NINE COHORT STUDIES OF BREAST IMPLANTS AND CONNECTIVE-TISSUE DISEASES.

STUDY	LOCATION AND YEAR	CATEGORY	NO. WITH BREAST IMPLANTS	NO. WITHOUT BREAST IMPLANTS	RELATIVE RISK (95% CI)*	ADJUSTMENT†
Edworthy et al.[10]‡	Alberta, Canada, 1998	All women	1576	727		Age, duration of exposure
		All definite connective-tissue diseases combined	19	16	1.0 (0.45–2.22)	
		Rheumatoid arthritis	11	6	1.44 (0.50–4.15)	
		Systemic lupus erythematosus	3	3	0.94 (0.17–5.23)	
		Scleroderma or systemic sclerosis	0	3	—	
		Sjögren's syndrome	5	4	0.99 (0.17–5.94)	
		Other conditions	36	36	—	
Friis et al.[11]§	Denmark, 1997	All women	2570	11,023		Age, calendar year
		All definite connective-tissue diseases combined	10	25	Not provided	
		Rheumatoid arthritis	7	16		
		Systemic lupus erythematosus	1	5		
		Scleroderma or systemic sclerosis	1	1		
		Sjögren's syndrome	1	1		
		Dermatomyositis or polymyositis	0	2		
		Other conditions	73	195		
Gabriel et al.[23]¶	Mayo Clinic, Rochester, Minn., 1994	All women	749	1,498		Age, year of diagnosis
		Women with any connective-tissue disease	5	10	1.10 (0.37–3.23)	
Giltay et al.[24]‖	The Netherlands, 1994	All women	235	210		Age
		Women with joint swelling	14	10	1.27 (0.55–2.92)	
Nyren et al.[15]**	Sweden, 1998	All women	7442	3,353		Age, follow-up time
		All definite connective-tissue diseases combined	16	11	0.8 (0.5–1.4)	
		Rheumatoid arthritis	11	5	1.3 (0.7–2.5)	
		Systemic lupus erythematosus	3	3	0.7 (0.3–1.6)	
		Scleroderma or systemic sclerosis	0	3	—	
		Sjögren's syndrome	1	0	—	
		Dermatomyositis or polymyositis	1	0	—	
		Other connective-tissue diseases	20	8	Not provided	
Park et al.[16]††	Scotland, 1998	All women	317	216		Indication for implant, age, stage of disease, date of surgery
		Women with rheumatoid arthritis	1	1	0.42 (0.01–15.63)	
Sánchez-Guerrero et al.[25]‡‡	United States, 1995	All women	1183	86,318		Age
		All definite connective-tissue diseases combined	3	513	0.6 (0.2–2.0)	
		Rheumatoid arthritis	3	389	0.9 (0.3–2.6)	
		Systemic lupus erythematosus	0	96	—	
		Scleroderma or systemic sclerosis	0	14	—	
		Sjögren's syndrome	0	2	—	
		Dermatomyositis or polymyositis	0	12	—	
		Other rheumatic conditions	29	4,541	Not provided	
Schusterman et al.[26]§§	Houston, 1993	All women	250	353		Indication for implant
		Women with rheumatic disease	1	1	1.08 (0.10–17.20)	
Wells et al.[27]¶¶	Tampa, Fla., 1994	All women	220	80		Age, year of surgery
		Women with arthritis	11	2	1.16 (0.15–9.04)	

*CI denotes confidence interval.

†Adjustments were made for the variables listed.

‡"Other conditions" included discoid lupus, Raynaud's phenomenon, CREST syndrome (consisting of calcinosis cutis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia), psoriatic arthritis, ankylosing spondylitis, Reiter's syndrome, fibromyalgia, osteoarthritis, hypothyroidism, multiple sclerosis, dermatomyositis or polymyositis, and Crohn's disease. A score for the degree of certainty of diagnosis was assigned, and any subject with more than 50 percent certainty of any possible condition was included in the analysis.

§"Other conditions" included polymyalgia rheumatica and temporal arteritis (as defined by the following codes from the *International Classification of Diseases, 8th Revision* [ICD-8]: 446.30–39); muscular rheumatism, fibrositis, and myalgia (ICD-8 codes 717.9 and 717.99); arthritis not further specified (ICD-8 code 715.99); rheumatism not further specified (ICD-8 code 718.99); and connective-tissue disease not further specified (ICD-8 codes 734.91 and 734.99). Ratios of observed cases to expected cases were calculated instead of estimates of relative risk.

¶"Any connective-tissue diseases" included rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, dermatomyositis or polymyositis, scleroderma or systemic sclerosis, ankylosing spondylitis, psoriatic arthritis, polymyalgia rheumatica, vasculitis, arthritis associated with inflammatory bowel disease, and polychondritis.

‖"Joint swelling" included any swelling of joints for at least one week.

**"Other connective-tissue diseases" included polymyositis (ICD-8 code 716.10, *International Classification of Diseases, 9th Revision* [ICD-9] code 710E), polymyalgia rheumatica (ICD-8 code 446.38, ICD-9 code 725), polyarteritis nodosa, temporal arteritis (ICD-8 code 446.30, ICD-9 code 446F), other specified connective-tissue disease (ICD-8 code 734.98, ICD-9 code 710W), connective-tissue disease or collagenosis without further specification (ICD-8 codes 734.91 and 734.99.10, ICD-9 code 710X), sarcoidosis (ICD-8 code 135, ICD-9 code 135), localized lupus (ICD-8 code 695.40, ICD-9 code 695E), ankylosing spondylitis (ICD-8 code 712.40, ICD-9 code 720A), fibromyalgia (ICD-8 codes 712.50, 717.98, and 718.99; ICD-9 code 729A), and psoriatic arthritis (ICD-8 code 696.00, ICD-9 codes 696A and 713D).

††Three of four groups in the study were retrospective cohorts; the fourth was a cross-sectional group.

‡‡"Other rheumatic conditions" included any rheumatic disease, musculoskeletal disease, connective-tissue disease not further specified, and any other form of arthritis (excluding osteoarthritis and fibromyalgia), as reported by patients.

§§"Rheumatic disease" included mild cases of autoimmune syndrome requiring therapy, without convincing laboratory findings for an absolute diagnosis of an autoimmune disease.

¶¶The diagnosis of arthritis was based on physicians' responses to a questionnaire.

TABLE 2. CHARACTERISTICS OF 11 CASE–CONTROL OR CROSS-SECTIONAL STUDIES OF BREAST IMPLANTS
AND CONNECTIVE-TISSUE DISEASES.

STUDY	LOCATION AND YEAR	CATEGORY	NO. OF CASES/ NO. WITH BREAST IMPLANTS	NO. OF CONTROLS/ NO. WITH BREAST IMPLANTS	ODDS RATIO (95% CI)*	ADJUSTMENT†
Burns et al.[28]	Michigan, 1996	Scleroderma or systemic sclerosis	274/2	1184/14	0.95 (0.21–4.36)	Age, birth year, race
Dugowson et al.[29]	Washington State, 1992	Rheumatoid arthritis	300/1	1456/12	0.41 (0.05–3.13)	Age
Englert et al.[30]	Australia, 1996	Scleroderma or systemic sclerosis	286/3	253/4	1.00 (0.16–6.16)	Socioeconomic status, age, ethnicity
Goldman et al.[34]‡	Atlanta, 1995	Rheumatoid arthritis and connective-tissue diseases	721/12	3508/138	0.52 (0.29–0.92)	Age at first visit to practice, income, time of first visit
		Rheumatoid arthritis	392/9		0.84 (0.41–1.62)	
		Systemic lupus erythematosus	180/1		0.14 (0.02–1.23)	
		Scleroderma or systemic sclerosis	64/0		—	
		Sjögren's syndrome	49/2		1.46 (0.36–6.39)	
		Dermatomyositis or polymyositis	36/0		—	
		Mixed connective-tissue disease	49/0		—	
Hennekens et al.[12]§	United States, including Puerto Rico, 1996	Any connective-tissue disease	11,805/231	383,738/ 10,599	1.24 (1.08–1.41)	Age, birth year
		Rheumatoid arthritis	6429/107		1.18 (0.97–1.43)	
		Systemic lupus erythematosus	1593/32		1.15 (0.81–1.63)	
		Scleroderma or systemic sclerosis	324/10		1.84 (0.98–3.46)	
		Sjögren's syndrome	774/22		1.49 (0.97–2.28)	
		Dermatomyositis or polymyositis	747/20		1.52 (0.97–2.37)	
		Other connective-tissue diseases	3354/83		1.30 (1.05–1.62)	
Hochberg et al.[31]	Baltimore; San Diego, Calif.; Pittsburgh, 1996	Scleroderma or systemic sclerosis	837/11	2507/31	1.07 (0.53–2.13)	Age, race, geographic site
Lacey et al.[13]	Ohio, 1997	Scleroderma or systemic sclerosis	189/1	1043/10	1.01 (0.13–8.15)	Age, birth year
Laing et al.[14]¶	Michigan, Ohio, 1996	Undifferentiated connective-tissue disease	205/3	2220/27	2.27 (0.67–7.71)	Age, birth year
Strom et al.[32]	Philadelphia, 1994	Systemic lupus erythematosus	133/1	100/0	—	Age
Teel[17]‖	Washington State, 1997	All connective-tissue diseases	427/6	1577/24	0.9 (0.4–2.3)	Age, year of diagnosis, race
		Systemic lupus erythematosus	191/2		0.8 (0.2–3.4)	
		Scleroderma or systemic sclerosis	55/0		—	
		Sjögren's syndrome	161/4		1.6 (0.5–4.7)	
		Dermatomyositis or polymyositis	17/0		—	
		Mixed connective-tissue disease	3/0		—	
Wolfe[33]	Kansas, 1995	Rheumatoid arthritis	637/3	1134/4	1.35 (0.30–6.06)	Age

*CI denotes confidence interval.

†Adjustments were made for the variables listed.

‡This study was cross-sectional. "Mixed connective-tissue disease" was defined according to ICD-9 codes 710.9 and 711. Six of 12 cases of connective-tissue disease were diagnosed before implantation.

§This study was cross-sectional. "Any connective-tissue disease" included all definite connective-tissue diseases and "other connective-tissue diseases." "Other connective-tissue disease" included mixed connective-tissue disease.

¶"Undifferentiated connective-tissue disease" was defined according to ICD-9 code 710.9. The diagnosis was assigned if the referring physician's diagnosis of the discharge code of Health Care Investment Analysts was undifferentiated connective-tissue disease or the patient had been given the diagnosis of scleroderma, but did not meet the criteria of the American College of Rheumatology; the patient did not meet the diagnostic criteria for another connective-tissue disease; and a minimum of two signs, symptoms, or laboratory values suggestive of a connective-tissue disease were documented.

‖The criteria for establishing a diagnosis of mixed connective-tissue disease were from the literature.

al studies[12,34] in our meta-analyses. The majority of the studies were conducted in the United States, but some were carried out in Canada,[10] Australia,[30] the United Kingdom,[16] and northern Europe.[11,15,24] The characteristics of the cohort studies are presented in Table 1, and those of the case–control and cross-sectional studies in Table 2. The cohort studies, the two cross-sectional studies, and one case–control study[17] evaluated multiple disease outcomes. The diagnosis of definite connective-tissue disease was obtained from medical records in all studies except that of Hennekens et al.,[12] which used self-reported data. The diagnosis of other autoimmune or rheumatic conditions

was obtained from medical records for all studies except four, which used self-reported data: Giltay et al.,[24] Hennekens et al.,[12] Sánchez-Guerrero et al.,[25] and Wells et al.[27] The 95 percent confidence intervals included 1 for all diseases in all studies, except that by Goldman et al.[34] (rheumatoid arthritis and connective-tissue diseases: adjusted relative risk, 0.52; 95 percent confidence interval, 0.29 to 0.92) and Hennekens et al.[12] (any connective-tissue disease: adjusted relative risk, 1.24; 95 percent confidence interval, 1.08 to 1.41; other connective-tissue diseases: adjusted relative risk, 1.30; 95 percent confidence interval, 1.05 to 1.62) (Table 2).

TABLE 3. ESTIMATES OF THE SUMMARY UNADJUSTED ODDS RATIO FOR THE ASSOCIATION BETWEEN BREAST IMPLANTS AND CONNECTIVE-TISSUE DISEASES.

DISEASE AND STUDIES INCLUDED IN ANALYSIS	NO. OF STUDIES	SUMMARY ODDS RATIO (95% CI)*	P VALUE FOR HOMOGENEITY†
All connective-tissue diseases combined			
All studies	16	0.69 (0.62–0.78)	0.10
All studies, excluding Friis et al.[11]	15	0.68 (0.60–0.77)	0.31
Rheumatoid arthritis	10	0.62 (0.52–0.73)	0.17
Systemic lupus erythematosus	8	0.63 (0.44–0.86)	0.24
Scleroderma or systemic sclerosis			
All studies	12	0.73 (0.46–1.10)	0.10
All studies, excluding Friis et al.[11]	11	0.70 (0.44–1.08)	0.14
Sjögren's syndrome	8	1.10 (0.74–1.58)	0.56
Dermatomyositis or polymyositis	6	0.90 (0.55–1.39)	0.88
Other autoimmune or rheumatic conditions			
All studies	12	0.91 (0.79–1.04)	<0.001
All studies, excluding Friis et al.[11] and Sánchez-Guerrero et al.[25]	10	0.92 (0.77–1.10)	0.52

*Conditional maximum-likelihood estimates are presented, except for the categories of all connective-tissue diseases combined and rheumatoid arthritis, for which estimates by the Mantel–Haenszel method are shown. Exact confidence intervals (CIs) are presented, except for the categories of all connective-tissue diseases combined and rheumatoid arthritis, for which limits obtained with the methods of Robins, Breslow, and Greenland are shown.

†Exact P values obtained by the method of Zelen are presented, except for the categories of all connective-tissue diseases combined, rheumatoid arthritis, and other autoimmune or rheumatic conditions, for which P values obtained with the Breslow–Day chi-square statistic are shown.

Table 3 presents estimated summary unadjusted odds ratios, 95 percent confidence intervals, and P values for the test for homogeneity for each of the conditions under study. For the evaluation of heterogeneity, the goal was to retain the largest number of studies that had statistical evidence of homogeneous estimates of effect, although we recognized that statistical analysis alone cannot rule out the possibility of persisting heterogeneity among those studies. The removal of the study by Friis et al.[11] from the analysis of all definite connective-tissue diseases combined and scleroderma or systemic sclerosis produced statistically homogeneous estimates; the removal of the studies by Friis et al.[11] and Sánchez-Guerrero et al.[25] from the analysis produced a homogeneous estimate for other autoimmune or rheumatic conditions. In all cases, the homogeneous estimate did not differ materially in size from the original estimate. In these unadjusted analyses, the estimates of the summary odds ratio were all less than 1, with the exception of that for Sjögren's syndrome: summary odds ratio, 1.10 (95 percent confidence interval, 0.74 to 1.58). For each of the conditions analyzed, the findings provided no evidence of an association between breast implants and specific connective-tissue diseases or combined connective-tissue diseases.

Table 4 provides two estimates of summary adjusted relative risk for each condition; one estimate includes the results of the study by Hennekens et al.,[12] and one does not. The large size of the study by Hennekens et al., as compared with each of the other studies, accounted for its disproportionate weight, which, in turn, created a summary estimate that is largely a reflection of the adjusted relative risk found in that study. When the study was included, the estimates of summary adjusted relative risk were slightly elevated for all connective-tissue diseases combined (1.14), rheumatoid arthritis (1.15), scleroderma or systemic sclerosis (1.30), Sjögren's syndrome (1.47), and other autoimmune or rheumatic conditions (1.15). The 95 percent confidence intervals included 1, except those for all connective-tissue diseases combined (1.01 to 1.28) and Sjögren's syndrome (1.01 to 2.14). When the study by Hennekens et al. was excluded, all estimates of summary adjusted relative risks were associated with 95 percent confidence intervals that included 1. The estimate of the summary adjusted relative risk of Sjögren's syndrome remained elevated (1.42), but the 95 percent confidence interval (0.65 to 3.11) clearly included 1.

The P values shown in the last column of Table 4 indicate whether the estimate of the adjusted relative risk from the study by Hennekens et al.[12] was significantly different from the summary estimate from the other studies.[21] For all definite connective-tissue diseases combined and other autoimmune or rheumatic conditions, the P values for this comparison were 0.003 and 0.08, respectively. These small values sug-

TABLE 4. ESTIMATES OF THE SUMMARY ADJUSTED RELATIVE RISKS OF AN ASSOCIATION
BETWEEN BREAST IMPLANTS AND CONNECTIVE-TISSUE DISEASES.

DISEASE AND STUDIES INCLUDED IN ANALYSIS	NO. OF STUDIES	SUMMARY ADJUSTED RELATIVE RISK (95% CI)*	P VALUE FOR HOMOGENEITY	WEIGHT OF HENNEKENS ET AL.[12] IN SUMMARY ADJUSTED RELATIVE RISK	P VALUE†
All connective-tissue diseases combined					
All studies	14	1.14 (1.01–1.28)	0.34	0.80	0.003
All studies, excluding Hennekens et al.[12]	13	0.80 (0.62–1.04)	0.92	—	
Rheumatoid arthritis					
All studies	8	1.15 (0.97–1.36)	0.90	0.79	0.56
All studies, excluding Hennekens et al.[12]	7	1.04 (0.72–1.51)	0.87	—	
Systemic lupus erythematosus					
All studies	5	1.01 (0.74–1.37)	0.33	0.77	0.12
All studies, excluding Hennekens et al.[12]	4	0.65 (0.35–1.23)	0.53	—	
Scleroderma or systemic sclerosis					
All studies	5	1.30 (0.86–1.96)	0.55	0.42	0.16
All studies, excluding Hennekens et al.[12]	4	1.01 (0.59–1.73)	0.80	—	
Sjögren's syndrome					
All studies	4	1.47 (1.01–2.14)	0.98	0.77	0.92
All studies, excluding Hennekens et al.[12]	3	1.42 (0.65–3.11)	0.90	—	
Dermatomyositis or polymyositis					
All studies	1	1.52 (0.97–2.37)	—	1.00	—
All studies, excluding Hennekens et al.[12]	—	—	—	—	
Other autoimmune or rheumatic conditions					
All studies	7	1.15 (0.97–1.36)	0.11	0.59	0.08
All studies, excluding Hennekens et al.[12]	6	0.96 (0.74–1.25)	0.19	—	

*CI denotes confidence interval.

†P values for grouped data were obtained with a chi-square test; this test assessed whether the estimate of the adjusted relative risk for the study by Hennekens et al.[12] was significantly different from the estimate of the summary adjusted relative risk for the other studies. Details about this global test for differences among groups can be found in Greenland.[21]

gest that the results were heterogeneous and further support our decision to perform separate meta-analyses with and without the data of Hennekens et al.[12] There is a distinct and important pattern in the size of the estimates of summary relative risk: the smallest in size are the unadjusted values, the next smallest are the adjusted values, excluding the results of Hennekens et al.,[12] and the largest values include the results of that study (Fig. 1). The results from the analysis of studies that included only silicone-gel–filled implants appear in Table 5. All the estimates of the summary adjusted relative risk were less than 1 for all conditions considered, and they were all lower than the corresponding estimates in Table 4.

DISCUSSION

We used several techniques of meta-analysis to evaluate the existing studies of the association between breast implants and connective-tissue diseases. These included both exact methods (unadjusted analysis)[22] and approximate, large-sample methods (adjusted analysis).[21] There is no evidence in either the analysis of unadjusted odds ratios or the analysis of adjusted relative risks, excluding the results of the study by Hennekens et al.,[12] of a significantly increased risk of any specific connective-tissue disease, all definite con-

nective-tissue diseases combined, or other autoimmune or rheumatic conditions. The estimated summary relative risks for scleroderma or systemic sclerosis, rheumatoid arthritis, and systemic lupus erythematosus are close to or less than 1. Although our estimate of the summary adjusted relative risk for Sjögren's syndrome (1.42; 95 percent confidence interval, 0.65 to 3.11) was elevated, a diagnosis of Sjögren's syndrome requires salivary-gland biopsy.[35] Whether biopsies were actually performed in the studies cited is unknown; and there may therefore have been bias in the size of the estimated summary adjusted relative risk due to misclassification of disease.

Our analyses showed that the summary adjusted relative risks that included the study by Hennekens et al.[12] were higher than the pooled results of the other studies for all definite connective-tissue diseases combined and for other autoimmune or rheumatic conditions. The study by Hennekens et al. was subject to various methodologic problems, including the lack of validation of disease diagnosis by review of the medical records. Self-reports of connective-tissue disease are inaccurate; in one study of self-reported rheumatoid arthritis, the positive predictive value was only 20 percent.[36] Furthermore, the intensive publicity about the postulated adverse health effects of breast

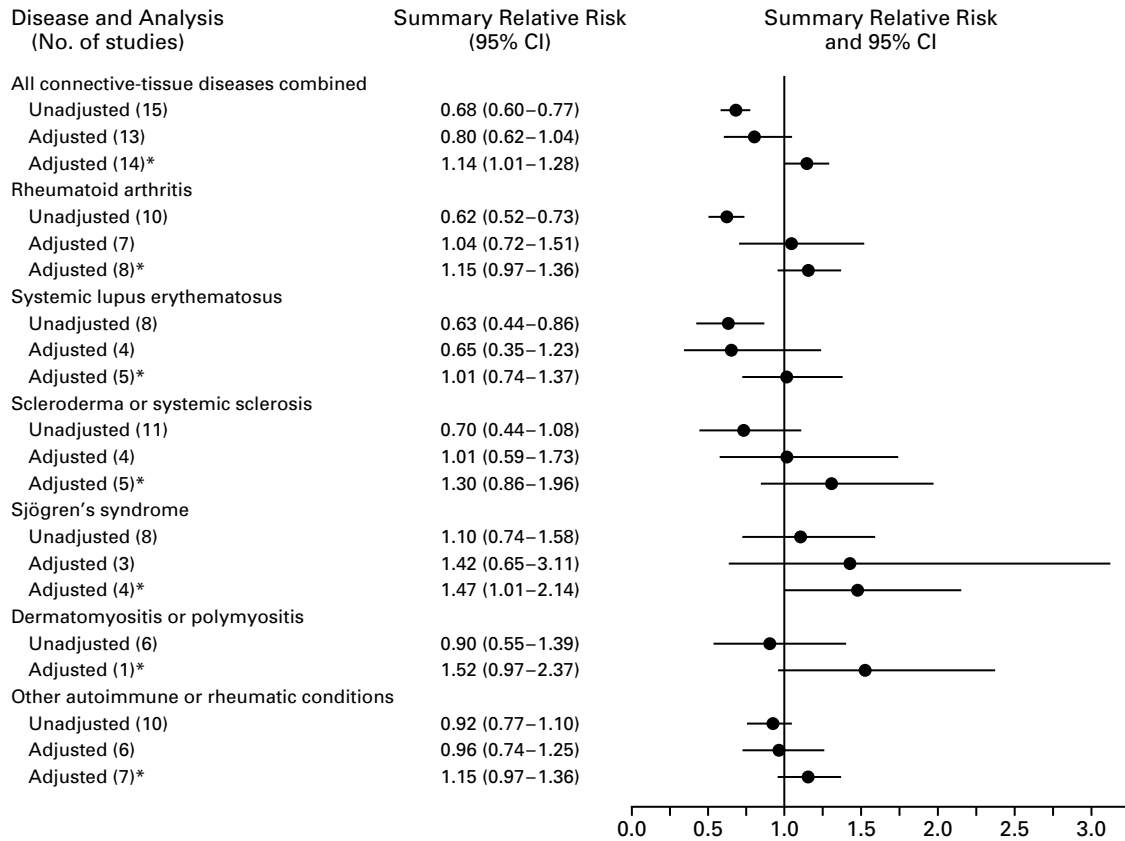| Disease and Analysis (No. of studies)	Summary Relative Risk (95% CI)	Summary Relative Risk and 95% CI
All connective-tissue diseases combined		
Unadjusted (15)	0.68 (0.60–0.77)	
Adjusted (13)	0.80 (0.62–1.04)	
Adjusted (14)*	1.14 (1.01–1.28)	
Rheumatoid arthritis		
Unadjusted (10)	0.62 (0.52–0.73)	
Adjusted (7)	1.04 (0.72–1.51)	
Adjusted (8)*	1.15 (0.97–1.36)	
Systemic lupus erythematosus		
Unadjusted (8)	0.63 (0.44–0.86)	
Adjusted (4)	0.65 (0.35–1.23)	
Adjusted (5)*	1.01 (0.74–1.37)	
Scleroderma or systemic sclerosis		
Unadjusted (11)	0.70 (0.44–1.08)	
Adjusted (4)	1.01 (0.59–1.73)	
Adjusted (5)*	1.30 (0.86–1.96)	
Sjögren's syndrome		
Unadjusted (8)	1.10 (0.74–1.58)	
Adjusted (3)	1.42 (0.65–3.11)	
Adjusted (4)*	1.47 (1.01–2.14)	
Dermatomyositis or polymyositis		
Unadjusted (6)	0.90 (0.55–1.39)	
Adjusted (1)*	1.52 (0.97–2.37)	
Other autoimmune or rheumatic conditions		
Unadjusted (10)	0.92 (0.77–1.10)	
Adjusted (6)	0.96 (0.74–1.25)	
Adjusted (7)*	1.15 (0.97–1.36)	

Figure 1. Comparison of the Estimates of Summary Relative Risk Obtained from the Unadjusted and Adjusted Meta-Analyses.

The solid circles denote the values for the summary unadjusted relative risk and two values for adjusted relative risk, one (indicated by the asterisks) including the study by Hennekens et al.[12] and one excluding it. The horizontal lines extending to the right and left of the black circles indicate the widths of the 95 percent confidence intervals (CIs). The variation in the confidence intervals is, for the most part, a function of the different sizes of the samples.

TABLE 5. ESTIMATES OF THE SUMMARY ADJUSTED RELATIVE RISKS OF AN ASSOCIATION BETWEEN SILICONE-GEL–FILLED BREAST IMPLANTS AND CONNECTIVE-TISSUE DISEASES.

DISEASE (STUDIES INCLUDED)	NO. OF STUDIES	SUMMARY ADJUSTED RELATIVE RISK (95% CI)*	P VALUE FOR HOMOGENEITY
All connective-tissue diseases combined (Burns et al.,[28] Edworthy et al.,[10] Englert et al.,[30] Lacey et al.,[13] Park et al.,[16] Sánchez-Guerrero et al.[25])	6	0.82 (0.46–1.46)	0.82
Rheumatoid arthritis (Edworthy et al.,[10] Park et al.,[16] Sánchez-Guerrero et al.[25])	3	0.98 (0.40–2.37)	0.43
Systemic lupus erythematosus (Edworthy et al.[10])	1	0.94 (0.17–5.23)	—
Scleroderma or systemic sclerosis (Burns et al.,[28] Englert et al.,[30] Lacey et al.[13])	3	0.85 (0.32–2.25)	0.70
Sjögren's syndrome (Edworthy et al.[10])	1	0.99 (0.17–5.94)	—
Other autoimmune or rheumatic conditions (Sánchez-Guerrero et al.,[25] Schusterman et al.[26])	2	0.61 (0.41–0.91)	0.68

*CI denotes confidence interval.

implants is likely to have made women with implants more aware of their symptoms and to have resulted in overreporting of disease among women with implants as compared with women without implants, thus potentially biasing the estimated effects upward. These factors suggest that the summary adjusted relative risks that included the study by Hennekens et al. were probably overestimates.

In general, the summary adjusted relative risks should be more valid than the summary unadjusted odds ratios. On the other hand, some of the studies with low estimates of relative risk were selectively excluded from the adjusted analysis because they had no cases of connective-tissue disease among women with breast implants. The summary adjusted relative risks calculated on the basis of the remaining studies could be higher as a result of bias.

Information on potential confounders of the association between breast implants and connective-tissue diseases was incomplete in many studies.[37] However, when potential confounding factors other than age, race, and year of study were evaluated, they had little effect on the adjusted relative risks reported in individual studies. Most of the specific connective-tissue diseases do not have strong established risk factors other than sex, age, and race.[38] Specific genetic markers of susceptibility are recognized for some of the connective-tissue diseases,[38-41] but no information on the basis of which to evaluate them was available in the epidemiologic studies. In addition, many studies did not report whether the indication for implantation was cosmetic or reconstructive, a difference that may have affected the signs and symptoms the subjects subsequently had. The two studies that included sufficient data to analyze the effect of long latency (10 or more years after implantation) on the incidence of connective-tissue disease suggested that the time since implantation was not predictive of the risk of connective-tissue disease.[12,25] Individual studies did not provide adequate data on rupture or leakage of implants for us to include these features as possible correlates of the incidence of connective-tissue disease.

Publication bias is frequently cited as a reason for lack of validity in meta-analyses.[42] Publication bias could occur if studies that found no association between exposure and disease were less likely to be submitted and accepted for publication than were studies that found a positive association. In fact, the results of the majority of the studies included in our meta-analyses were negative, as stated by the authors. Nonetheless, we examined the potential for publication bias by constructing a funnel plot in which the inverse of the estimated variance of the natural logarithm of the adjusted relative risk was plotted against the natural logarithm of the adjusted relative risk for each disease.[42] Funnel plots of our data showed no evidence of publication bias for any of the disease entities we studied (data not shown).

Given the results of the individual studies and our summary adjusted relative risks, we do not have convincing evidence that the underlying summary relative risk of connective-tissue disease in the population of women with breast implants exceeds 1. On the basis of calculations in which the standard errors from the studies under consideration were used, our study had approximately 80 to 90 percent power to detect true summary relative risks of 1.5 to 2.0, when all studies were included.[18] However, when the study by Hennekens et al.[12] was excluded, the power of the study to detect a summary relative risk ≤2.0 was roughly 70 percent or less for scleroderma or systemic sclerosis, systemic lupus erythematosus, and Sjögren's syndrome.[18]

We calculated the population attributable risk, the proportion of cases of connective-tissue disease in a population that may be caused by breast implants, using standard formulas.[43,44] To estimate the number of cases of connective-tissue disease attributable to implants, we used the summary adjusted relative risks obtained from our meta-analyses that included the study by Hennekens et al.,[12] assumed the proportion of women with breast implants in the United States to be 1 percent, and multiplied the annual incidence of disease (averages obtained from reports in the literature[17,25,40,45-57]) by the population attributable fraction. Although we chose high estimates for the proportion of women with breast implants and the summary adjusted relative risks so as to maximize the possible public health effect of breast implants in our calculations, the estimated annual number of new cases of connective-tissue disease that could be attributed to breast implants was small. Among 10 million women in the United States, 4.3 of 3303 new cases of rheumatoid arthritis, approximately 0.1 of 526 new cases of systemic lupus erythematosus, 0.4 of 164 new cases of scleroderma or systemic sclerosis, 1.3 of 400 new cases of Sjögren's syndrome, and 0.2 of 54 new cases of dermatomyositis or polymyositis may be attributed to breast implants each year.

Despite the differences in the meta-analyses conducted thus far, none, including the meta-analyses reported here, have identified a significant association between breast implants and connective-tissue diseases. On the basis of the research to date, no association is evident between breast implants and any of the individual connective-tissue diseases, all connective-tissue diseases combined, or the other autoimmune or rheumatic conditions, with the possible exception of Sjögren's syndrome. The uncertainty of the diagnosis of Sjögren's syndrome makes the interpretation of the estimated summary adjusted relative risk questionable, however. The meta-analysis focusing solely on silicone-gel–filled implants produced lower summary estimates of the adjusted relative risks for all the diseases than did the analyses based on all types of breast implant. From a public health perspec-

tive, breast implants appear to have a minimal effect on the number of women in whom connective-tissue diseases develop, and elimination of implants would be unlikely to reduce the incidence of connective-tissue diseases.

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